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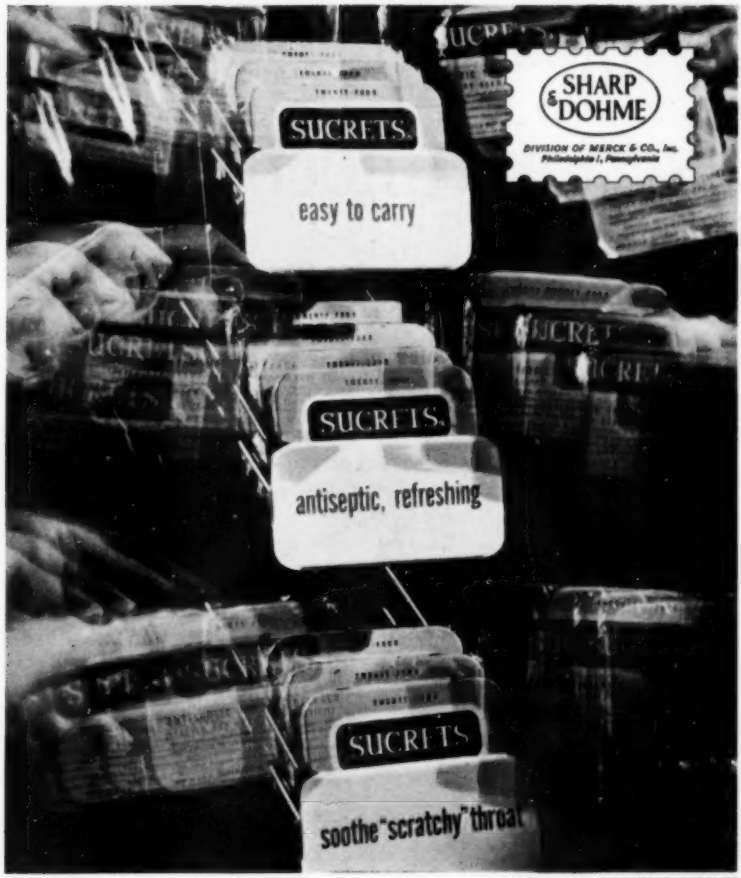

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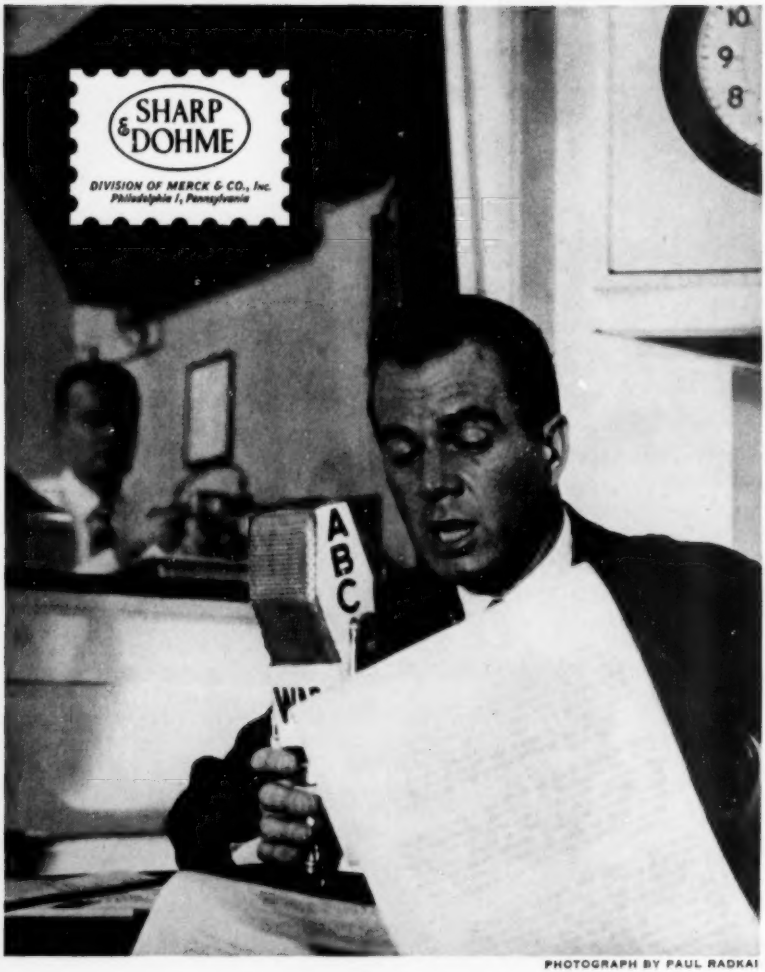

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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EDITORIAL

EDUCATION FOR MEDIOCRITY

AMONG the various activities engaged in by the editor are those of counseling college students majoring in pharmacy and some of its related sciences. That there has been a gradual but profound change in the last two decades in the nature of the raw material entering American colleges is a deepening and disturbing conviction—disturbing since the change is not all for the better.

At one time a high school education was not possible for all who sought it, since either economic or scholastic limitations precluded its accomplishment. Today, almost everyone is assured a high school diploma. Economic pressures are less, school attendance is required, and failure to graduate is a social stigma.

All this is fine indeed for every reasonably normal boy and girl deserves this minimum of 12 years schooling and no one would wish it otherwise. There are, however, certain complications resulting from this education of the masses which promise to impair greatly our future progress particularly in science and engineering, two areas in which our record and standing as a nation are being seriously challenged by Soviet Russia.

Our public schools have been so busy trying to meet the problems of mass education that certain of their primary responsibilities have suffered serious neglect. One of these is the necessity of providing the mental gymnastics, so to speak, required to develop young minds and brains to their peak efficiency. There is every reason to believe that many of our most intelligent young people succeed in going through high school without once meeting a scholastic challenge of such magnitude as to require their best performance for a protracted period.

While the brain functions differently than our muscles, there is no doubt but that learning to solve difficult problems increases brain power just as exercise strengthens the muscles. It is a mentally flaccid youth today who usually emerges from school, pathetically and tragically unaware of his unpreparedness to face the difficult tasks imposed by higher education. As a result the first college year is

often a harrowing and disheartening experience. The work load seems impossible to accomplish and the performance required beyond human endurance. The student cannot grasp the reason for his failure. This is the explanation of the high mortality rate of college freshmen—they have never learned to work hard, and their poor study habits and satisfaction with mediocrity, permitted until now, has all but destroyed their energy and initiative towards difficult tasks.

The secondary schools shrug off the responsibility of this and talk about the need for group action, social consciousness, an appreciation of democratic ideals and institutions, etc.—to which all must agree. But can this be achieved only by the sacrifice of our most capable youth? Our school authorities would have the colleges solve this problem by giving special pre-college level courses pointing out that only a minority attend college in the first place and their responsibility is to all.

This is a poor solution because learning to use one's brain must come early in life not in the late teens. There is, furthermore, so much complex material that must be mastered in college that there is not time to reconstruct the damage done in high school if in truth it can be done at all.

Possibly we have carried our processes of democracy too far in the public school, in that we have placed a premium on mediocrity and made this the standard to which all are encouraged to conform. If so, then our scientific and technologic supremacy will not long endure.

Russia with all its distasteful methods at least sets a high standard for bright young children in its schools. As a result, they outmatch us in qualified candidates for the more difficult disciplines of science and are in fact training more specialists in science and engineering than we are. There, life is a stern business as youth well knows and they face its hardships and difficulties with determination. Here we adapt the circumstances and conditions faced by our children in school to that level compatible with nights of television, movies, juke-boxes and comics. After all we are the greatest country on earth; we deserve lives of ease and will tolerate nothing difficult or burdensome, else we will complain to our chosen representatives. Who, after all, is there to challenge our position in the sun? Who indeed!

L. F. Tice

CHEMOTHERAPY IN INFECTIOUS DISEASES *

By Henry Welch **

IN the past twelve years we have seen the birth and growth of a huge new antibiotic industry. Non-existent in 1943 it now has a capital value measured in hundreds of millions of dollars. The antibiotic drugs it produces have completely modified basic medical teachings in universities and schools of medicine. Previously established concepts of the treatment of infectious diseases have had to be changed and the natural history of infections, antibiotic effects on fever cycles and immunological responses to antigenic stimuli are gradually being reappraised.

It has been an exciting and educational experience to watch the development of this young and vigorous industry. Back in 1943 we had some twenty manufacturers producing penicillin largely by the "bottle" method. Each manufacturer gambled on the future of this then unknown and untried drug. Some 29 pounds of crude pencillin were produced that year.

ANTIBIOTIC PRODUCTION

Year	*Antibiotic*	*Lbs.*	*Kg.*	*Approximate*
1943	Penicillin	29	13	$ 3,000,000
1944	Penicillin	3,200	1,455	
1945	Penicillin	14,000	6,364	
1951	Penicillin	636,000	289,091	137,000,000
1953	Penicillin	756,600	343,909	58,000,000
1946	Streptomycin	3,800	1,727	11,400,000
1953	Streptomycin & DHSM	375,200	170,545	35,000,000

* Presented at the Columbia Bicentennial Conference October 15, 1954.

** Director, Division of Antibiotics, Food and Drug Administration, Department of Health, Education, and Welfare.

Year	*Antibiotic*	*Lbs.*	*Kg.*	*Approximate*
1953	Broad Spectrum	417,600	189,818	137,000,000
	Chlortetracycline			
	Oxytetracycline			
	Tetracycline			
	Chloramphenicol			
	Feed Supplements	434,000	197,273	19,000,000
1953	TOTAL ALL ANTIBIOTICS (est.)	2,000,000	909,091	$262,000,000

The scarcity of penicillin made it necessary in many cases to collect the urine from treated patients and re-extract it for use on others.

In 1944 production jumped tremendously and over 3,000 lbs. of the crude drug was made available. None of the drug was released to civilians except for a few "pathetic appeal" cases until 1945, when through the manufacturing ingenuity of the chemical and pharmaceutical industry some seven tons of penicillin were produced. Our armed forces and those of our allies who received all of the drug produced until 1945 used it to great advantage. The high cost of production made penicillin much more valuable than gold and 100,000 units or 60 mgs. cost $20.00. The 29 pounds produced in 1943 was worth $3,000,000. Ten years later 756,000 pounds of the crystalline drug was valued at $58,000,000. Another very great change in the value of penicillin took place between 1951 and 1953. In the former year some 600,000 pounds had a value of $137,000,000 while in 1953, 750,000 pounds was valued at only $50,000,000. The armed forces who paid $20.00 for each 100,000 units in 1943 purchased this amount in 1953 for approximately two cents. This tremendous drop in the cost of penicillin has been the result of marked improvements in yields and manufacturing methods, in a highly competitive industry.

The story of streptomycin which first became available in quantity in 1946 has been of a similar nature. About 3800 pounds were produced in 1946 and this had a value of about eleven million dollars. One hundred times as much (375,000 pounds) was produced in 1953 yet its value was only $35,000,000. The price of this drug originally at fifteen dollars a gram is now on the order of fifteen cents.

The broad spectrum drugs, chlortetracycline, oxytetracycline, tetracycline and chloramphenicol were also produced in great quantity in 1953—over 417,000 pounds—with an estimated value of $137,000,000.

In addition to the production of antibiotics for pharmaceutical uses there has been a wide use of some of these drugs, largely chlortetracycline, oxytetracycline, and penicillin in the manufacture of animal feed supplements. Over 439,000 pounds were produced for this purpose in 1953. Thus a total of 2,000,000 pounds of antibiotics were produced in the United States in 1953 with a value of about $262,000,000 by an industry which came into existence only a few short years ago.

Upwards of 3500 different antibiotic substances have been isolated and studied since 1942 and although the great majority have not been found useful because of low potency or high toxicity, an average of one each year has proven of value, therapeutically.

USEFUL ANTIBIOTICS AND YEAR INTRODUCED

Penicillin	1929-1943	Neomycin	1949
Tyrothricin	1939	Fumagillin	1950
Streptomycin	1943	Oxytetracycline	1950
Bacitracin	1945	Viomycin	1950
Chloramphenicol	1947	Erythromycin	1952
Polymyxin	1947	Carbomycin	1952
Dihydrostreptomycin	1948	Tetracycline	1953
Chlortetracycline	1948		

Following penicillin which was found to be of greatest value against diseases caused by gram-positive organisms, streptomycin was discovered and although of value against gram-negative organisms, its greatest usefulness was shown to be in the treatment of tuberculosis. With the discovery and later synthesis of chloramphenicol we had our first so-called broad spectrum antibiotic. This drug was found not only to be active against gram-positive and gram-negative organisms, but certain large viruses and rickettsia as well. Rapidly following the development of chloramphenicol was the first of the tetracyclines, chlortetracycline, then called Aureomycin when its structure was unknown. Two years later Terramycin, later called oxytetracycline, was isolated and finally the third of the tetracyclines, tetracycline itself, was produced in the laboratory by dechlorination of Aureomycin. It was rapidly shown, however, that tetracycline could be produced by fermentation of a *Streptomyces species* as well as by hydrogenation of chlortetracycline.

These six antibiotics, penicillin, streptomycin, chloramphenicol, tetracycline, chlortetracycline, and oxytetracycline, form the bulwark of our fight against infectious diseases.

DISEASES AMENABLE TO ANTIBIOTICS

- Pneumococcal and streptococcal infections
- Staphylococcus infections
- Meningococcal and gonococcal infections
- Treponemal diseases
  - Syphilis
  - Yaws
  - Pinta
  - Bejel
- Other spirochetal diseases
  - Weil's disease
  - Vincent's angina
  - Relapsing fever
  - Tropical ulcer
- Surgical infections
- Urinary and intestinal tract infections
- Brucellosis, plague, and tularemia
- Tuberculosis
- Granuloma inguinale
- Chancroid
- Carrion's disease
- Pertussis
- Diptheria
- Hemophilus influenza meningitis
- Infectious mononucleosis
- Anthrax
- Actinomycosis
- Nocardiosis
- Blastomycosis
- Trichomonas vaginalis vaginitis
- Rat bite fever
- Virus diseases
  - Psittacosis
  - Lymphogranuloma venereum
  - Trachoma

Inclusion conjunctivitis
Epidemic keratoconjunctivitis
Primary atypical pneumonia
Rickettsial diseases
Rocky Mountain spotted fever
Epidemic and endemic typhus
Rickettsialpox
Scrub typhus
Q fever

With these drugs the spectrum of amenable diseases has widened almost yearly. We control to a large extent pneumococcal and streptococcal infections, meningococcal and gonococcal infections, staphylococcal infections, syphilis, yaws, pinta, bejel, Weil's Disease, relapsing fever, tropical ulcer, Vincent's angina, surgical infections, urinary and intestinal tract infections including amebiasis; brucellosis, plague, tularemia, tuberculosis; diseases due to certain large viruses and rickettsia, including primary atypical pneumonia, psittacosis, lymphogranuloma venereum, trachoma, Rocky Mountain spotted fever, epidemic and endemic typhus, scrum typhus and Q fever. Other diseases also largely under control are: granuloma inguinale, chancroid, Carrion's disease, pertussis, diptheria, influenzal meningitis, anthrax, actinomycosis, trichomonas vaginalis vaginitis and rat bite fever. In addition to these specific infections, antibiotics have found wide use in ophthalmology, and in oral surgery and dentistry.

This indeed is an imposing list of infections that are either completely or partially controlled by the six antibiotics noted above. However, a second line of defense against a variety of infections is also available to us. Tyrothricin, bacitracin, polymyxin, neomycin, viomycin, erythromycin, carbomycin, and fumagillin all have a place in the physician's armamentarium. These fill in many of the gaps where the others fail. Furthermore, new antibiotics just becoming available such as fungicidin, anisomycin and puromycin may add further ammunition in our war against infectious diseases.

One of the outstanding successes of the antibiotics and particularly penicillin is the control of subacute bacterial endocarditis. This disease was nearly always fatal prior to penicillin. It was not reduced by more than 2.5 per cent with the sulfonamides. In con-

trast, when penicillin is used in adequate amounts the mortality rate of practically 100% is reduced to from 25 to 30 per cent.

The fatality rate of pneumococcic pneumonia was 30 to 33 per cent prior to serum treatment and the sulfa drugs. Specific antisera reduced the over-all death rate to about 17 per cent while the sulfonamides reduced the rate to about 12 per cent. With the use of penicillin and the other antibiotics in this disease the fatality rate has dropped to about 5 per cent.

The fatality rate in scarlet fever before sulfonamides was probably 2 to 5 per cent and this was not diminished by these drugs. Following adequate and early treatment with antibiotics the fatality rate for all practical purposes is zero. Transmission of the disease is definitely inhibited and this applies to other hemolytic streptococcal infections as well. Rheumatic fever, a serious and incapacitating disease with its high mortality rate due to residual heart damage, is largely controlled through the prophylactic use of penicillin. The prevention of recurrent attacks by the prophylactic use of penicillin will result in a markedly reduced mortality rate and allow those afflicted more freedom of action and a greater range of activity.

Two hundred years ago Sir Richard Morton prescribed as follows for the treatment of tuberculosis:

> "Take of new milk two Gallons, distil it with Mint, Roman Wormwood, of each two Handfuls to a Gallon. Then take of Garden Snails, washed first in common Water, and then Small Beer, half a Peck; of Earth Worms, slit and wash'd; a Pint, of Angelica, a Handful and half, Agrimony, Betony, Rue; of each, a Handful. Put the herbs in the bottom; upon these lay the Snails and Earthworms, and upon the top of all, lay of Shavings of Hartshorn, half a Pound, of Cloves an once, of Saffran three Drams; Infuse them in two Quarts of Syder, and a Quart of the best Malaga Sack, and then distil them in ordinary Still. These liquors must be drank plentifully."

This prescription was for the cure of consumption in the second degree. We have come a long way since then for some two hundred years later specific drugs directed against the etiological agent have markedly changed the mortality rate of the "white plague."

With the discovery of streptomycin a new age of progress in the treatment of tuberculosis was initiated. Later developments which

allowed combined therapy with para-amino salicylic acid and isoniazide further improved the chemotherapy of this disease. It is true that the death rate from tuberculosis has been decreasing since 1900 and one has to depend upon changes in the gradient of this fall to reach a conclusion as to the effect of chemotherapy on the death rate but with a reported fall of 50 per cent in the Veterans Administration hospital death rate since 1946 one can, I believe conclude that these specific agents have had their impact on mortality from tuberculosis. The fact that waiting lists for admission to Veterans Administration hospitals has fallen approximately 2500 in 1946 to 200 in 1954 is not without significance. Furthermore, other effects of chemotherapy are quite impressive. Definitive surgery can now be performed on patients who otherwise would be ineligible for it and there is a markedly decreased number of post operation difficulties. For all practical purposes complications of pulmonary tuberculosis such as enteritis, laryngitis, and tracheobronchial involvement have disappeared. Meningeal and miliary tuberculosis before chemotherapy were invariably fatal. The dramatic reversal to a survival rate of 80 per cent attests to the efficacy of these important drugs. One can say that the introduction of chemotherapy has made possible the disappearance of tuberculosis as a substantial cause of death in the United States. It is only necessary in the care of tuberculosis as has been recommended for wives. "Catch them young" (diagnose the disease early) "treat them rough" (use adequate chemotherapy and its adjuncts) and there seems to be no reason why this should not again become a male paradise.

One of the outstanding conquests of a serious disease by penicillin is that of syphilis. This drug has made such inroads on this disease that it is most difficult to find in a given community a sufficient number of cases of primary syphilis for experimental studies. Practically all syphilologists have discarded the heavy metals and rely on penicillin alone for syphilis therapy because of the ease of administration, its safety, the shortened course and the low cost of treatment. The accumulated experience of many physicians and numerous clinics treating hundreds of thousands of patients clearly indicate that penicillin alone is the treatment of choice in all types of syphilis and for that matter uncomplicated gonorrhea as well. With the development of the newer repository forms of penicillin it has been demonstrated that a single injection of 1.2 to 2.4 million units is adequate

for the treatment of early syphilis and the non-venereal treponematoses including yaws, bejel and pinta. It is now possible to cure these diseases in a short period of time at low cost. There is no reason why millions of people throughout the world need to be affected and subsequently develop the crippling and killing sequelae of either gonorrhea or syphilis.

In this world of ours we are constantly faced with a "balance in nature." We make steps forward, sometimes great strides, only to be thrown backwards by unforeseen difficulties. It has not been different with antibiotics. In spite of the antibiotic saga of battles won over many of the infectious diseases the "golden bullets" have sometimes proven to be "duds" and have succeeded only in complicating our problems or giving us new ones with which we must contend.

With increasing use of antibiotic drugs and particularly penicillin we are encountering more and more resistant microorganisms. Particularly is this true of the staphylococci which are becoming of more importance daily especially in hospital practice.

Increasing numbers of patients with serious infections that are presumably due to antibiotic-sensitive organisms show temporary improvement under specifically directed antibiotic therapy only to be followed by infections of the same or other organs or tissues with staphylococci that are resistant to the antibiotics that were originally used. Other organisms such as Proteus, Pseudomonas and the Enterococcus are also encountered under similar circumstances but are probably less important. The range of antibiotics to which the staphylococci are acquiring resistance has increased and now includes penicillin, streptomycin, the three tetracyclines and erythromycin, and some strains resistant to chloramphenicol are also being encountered. It may be assumed that erythromycin-resistant strains are also resistant to carbomycin, perhaps even more so than to erythromycin. These staphylococci presumably originate in the first instance by passage through patients who have been treated with these various antibiotics and the resistance pattern of the staphylococcus presumably varies with the practices and prejudices of the particular hospital with respect to the choice of antibiotics and the frequency with which they are used. The use of antibiotics in combinations in individual patients has helped to delay the occurrence of this phenomenon, but has not entirely eliminated it.

A portion of the tremendous production of antibiotic drugs has been directed to the prophylaxis and treatment of animal diseases.

Further extension of the uses of these drugs in animal nutrition, to increase the rate of growth, as crop sprays, and possibly food preservatives can seriously complicate the task of the medical profession.

EXTENSION OF USES OF ANTIBIOTICS

In Nutrition:
- Swine, chicks, poults

In Animals:
- Therapeutic, prophylactic uses.
  - Cows, beef cattle, calves, swine, chicks, Mink

As Crop Sprays:
- Blight:
  - Apple, pear, walnut, peach, beans
- Bacterial Diseases:
  - Tobacco, tomatoes, pepper, cherries, Spinach, lettuce, potatoes

As Food Preservatives:
- Vegetables, hamburger, cream fillings, fish, fish fillets, shrimp, beer fermentation, Beef carcasses, chickens, etc.

Following treatment of mastitis in cows with antibiotics it is common to find significant amounts of the drug in the milk of the animal for days and even weeks after treatment. Unless adequately controlled, antibiotic sprays for crops could possibly reach the consumer and in significant quantities if these drugs are used extensively. This problem would be further complicated if antibiotics were to be used widely as food preservatives. Certainly those who are sensitive to one or more of these drugs could well be apprehensive.

Unfortunately the wide and perhaps sometimes unwise use of antibiotics has increased the number of individuals sensitive to them. The diversion on occasion of veterinary preparations that are sold without prescription for human use has not helped this problem. The pharmacist plays an important role in preventing such sometimes dangerous, unsupervised use.

The results of a spot survey of the United States, completed in 1953, of acute anaphylactoid reactions to antibiotics is quite informative.

ACUTE ANAPHYLACTOID REACTIONS TO PENICILLIN

Type of Product	*Reactions*	*Fatal*
Procaine Penicillin (Injection)	55	18
Penethamate (Diethylaminoethyl ester hydriodide) (Injection)	26	5
Penicillin 'O' (Injection)	2	0
Dibenzylethylenediamine Dipenicillin G (Oral, Tablet)	1	1
	84	24

(Four reactions from Streptomycin, 3 following intrathecal injection, one of which was fatal, one followed an intramuscular injection, recovered.)
(17 reported in literature exclusive of above.)

Only one of the 84 penicillin reactions recorded in this survey followed administration of an oral preparation. Procaine penicillin, the most commonly used of the penicillin salts was responsible for 55 reactions and 18 deaths. Penethamate, an hydriodide ester of penicillin used very infrequently as compared to procaine penicillin, accounted for another 26 of the 84 anaphylactoid reactions, while pencillin 'O' (allylmercapto methyl penicillin) a penicillin which appears to have a lower sensitizing potential, resulted in two reactions, neither of which was fatal. It is of interest that although the survey covered all anaphylactoid reactions due to antibiotics, none were found resulting from broad spectrum drugs, (chloretetracycline, oxytetracycline, and chloramphenicol) and only four followed injection of streptomycin. In addition to the 88 anaphylactoid reactions reported in the survey referred to, we know of 17 others reported in the literature. With the recognition that a number of such reactions are not reported, it can be assumed that we have in this country from 100 to 200 anaphylactoid reactions yearly following administration of penicillin.

There is reason to believe that the repository type of penicillin preparation is more prone to sensitize than the soluble salts in aqueous solutions. With some of the insoluble salts the drug is in contact with tissue for days and even weeks. The longer the time interval that penicillin is in contact with body tissue the more likely the production of partial antigens. These in turn can act as antigenic stimuli for antibody production.

Potassium penicillin, like the sodium salt, reaches a high level rather rapidly after injection, and is excreted in a matter of hours. Procaine penicillin having a lower solubility in water is held in the tissues longer (about 24 hours) but the peak level is lower. A somewhat less soluble salt, benzylamine penicillin, acts in somewhat the same manner. The addition of a thixotropic gel of 2% aluminum monostearate in vegetable oil to procaine penicillin further prolongs blood concentrations for up to four days, but the concentration in the blood is correspondingly low. Very low concentrations of penicillin are obtained following injection of one of the newest of the repository penicillins, dibenzylethylenediamine dipenicillin (DBED) but measurable amounts are observed for a week after an intramuscular injection of 300,000 units. Following injection of 1,200,000 units of this salt, penicillin is found in the blood for four weeks in most patients. The repository penicillin preparations are of great value in venereal diseases and in the prophylaxis of certain infections. However, in asthmatics or in those individuals with a history of allergy these preparations should be used with caution.

The tetracyclines are not prone to sensitize readily. An occasional rare case of sensitivity has been reported but none of the anaphylactic type of reaction was observed in the survey referred to above. These drugs are administered in the great bulk of cases orally and this may be a factor in the low incidence of allergic reactions seen. Certainly, since tons of these drugs have been used the low sensitizing potential is not associated with lack of use.

In addition to the frank sensitizing potential of the antibiotic drugs, during the past few years we have encountered a more subtle sensitization phenomenon, perhaps better called an idiosyncrasy. The blood dyscrasias shown to follow use of chloramphenicol in certain individuals is not due to an inherent toxicity of this antibiotic but rather is related to its ability to sensitize certain individuals to later administration of the drug. The tons of chloramphenicol used in hundreds of thousands of individuals attests to the innocuousness of it in the great majority of individuals and argues strongly against an inherent toxicity.

When chloramphenicol was first studied, and for a long time thereafter, it was considered to be the least toxic of the broad spectrum drugs, at least from the standpoint of gastrointestinal disturbances. It was this low incidence of side reactions that may have provoked

its wide and perhaps unwise use in some instances. However, it should have been recognized that as a drug of considerable potency and potential for good, it, of necessity, could be harmful under appropriate conditions in certain individuals.

Surveys of the country, including a total of 45 states, were made in both 1952 and 1953 to determine the extent of the problem of blood dyscrasias following the use of potent drugs with particular emphasis on chloramphenicol.

BLOOD DYSCRASIAS SURVEY

1952-53

A. Chloramphenicol only	84	68*
B. Chloramphenicol and other drugs	230	148*
C. Chloramphenicol not involved	1446	403*
	1760	619

Total cases reviewed: 1987

227 cases discarded. No evidence of actual blood dyscrasia or insufficient data.

* aplastic anemia.

Of nearly 2,000 cases reviewed only 84 could be shown to have followed use of chloramphenicol. Following concomitant use of chloramphenicol and other drugs a total of 230 cases were found but 1446 blood dyscrasias were found in which chloramphenicol was not involved. The list of drugs apparently associated with these latter dyscrasias reads like the Pharmacopia or National Formulary. As far as chloramphenicol is concerned, assuming this drug caused all cases that were treated with chloramphenicol, whether other drugs were used or not, the incidence appears to be on the order of 1 in 20,000.

There seems to be no question that on rare occasions under certain conditions chloramphenicol can cause serious blood dyscrasias. It is to be regretted that we cannot now define these "conditions" but repeated exposure does appear to carry an increased hazard. Furthermore, children under 10 years of age are most frequently affected and females are more prone to develop a blood dyscrasia than males in a proportion of about three to one.

There is a general agreement that penicillin is probably the least toxic of the potent chemotherapeutic agents now in use, yet we have reason to believe that it is responsible for from 100 to 200 anaphylactic-like reactions in a single year and the number appears to be increasing. While it is true that in this anaphylactoid-type of reaction an adequate history and sensitivity tests may afford a means of prevention, these are not infallible. It must be concluded that the decision to use chloramphenicol or penicillin, or for that matter any potent drug, must rest with the physician who through clinical judgment balances the drug's potential to do harm against the seriousness of the condition under treatment. The pharmacist has a responsibility in handling such antibiotic drugs. All are potent and all have a potential to do harm. The pharmacist is the barrier between these prescription drugs and the "self medicators" who like to play "doctor" but in effect "know not what they do."

In this discussion an attempt has been made to outline briefly the development of a great industry. The impact the antibiotics produced have had on a broad group of serious infections and the changes in chemotherapy resulting have been presented. Against the advances made in our war with the infectious diseases the problems that have made life more complicated have been touched on. In spite of our improvements in the chemotherapy of a long list of diseases there is still much to be done. We have not overcome the problem of proteus and pseudomonas infections. Although we have accomplished much with tuberculosis there is still great room for improvement. We need now a reduction in the morbidity of this disease. We have failed completely to find a solution in those diseases caused by the small viruses. However, we have reason to be optimistic. Some of the newer antibiotics have definite anti-tumor and anti-carcinogenic effects. Much has been accomplished in the past decade and there is no sound scientific basis for believing we will be unable to find in the next decade antagonistic substances in nature that will make it possible to further widen the spectrum of diseases and thus include those that, at the moment, escape us.

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A CRITICAL EVALUATION OF FLUORIDATION

By Charles A. Brusch,* B.S., M.D. and
George B. Ceresia,** Ph.D.

EDITOR'S NOTE:

It is the editor's opinion that a good case has been made in support of the fluoridation of municipal water supplies, but it is the policy of this journal to print both sides of any controversy when the proponents are responsible and capable workers. The arguments against fluoridation are well summarized in this paper.

THE recent hearings on the Weir Bill (1) to prevent fluoridation by cities on a national scale has aired some of the pros and cons of this controversy. While there exists a multiplicity of data showing that addition of fluorine to drinking water is largely beneficial in delaying tooth decay, there has been a great deal of contradictory evidence and sworn testimony by experts concerning its adverse affects on the physiological system (2). At the risk of being included in the group which "presents arguments against adding one part per million of sodium fluoride to drinking water resembling those raised fifty years ago against chlorination of water, against pasteurization and against vaccination" (3), this article is designed to critically review and present the liabilities of fluoridation as revealed by recent scientific investigation.

The relationship between the fluoride ion and dental health starts with an inquisitive dentist, F. S. McKay in Colorado Springs. He observed characteristic brown stains on the teeth of so many patients that he became curious. He consulted with a dental pathologist by the name of G. V. Black and, in 1915, they both published a paper describing "mottled enamel" in teeth. Dr. Black died soon after, but Dr. McKay continued searching and approximately fifteen years later found his answer, fluorine content of the drinking water.

* Director of the Brusch Medical Center, Cambridge, Mass.

** Asst. Professor of Chemistry, Albany College of Pharmacy, Union University, Albany, N. Y.

In 1931 the chief chemist for Alcoa studied the water of Bauxite, Arizona, and found the drinking water contained fourteen parts per million of fluoride which he ascribed as the cause of the brown stain on the inhabitants teeth. Simultaneously, an independent investigation by Margaret C. and H. V. Smith, University of Arizona chemists, found by animal experimentation and chemical analysis of the water of Saint David, Arizona, that fluoride concentration had a toxic effect on the teeth, called "mottling."

Facts such as this led H. T. Dean, now director of the National Institute of Dental Research, and his associates into carrying out a study of the effect of fluoridated and non-fluoridated waters on the teeth (4). Examining the mouths of seven thousand children ranging from twelve to fourteen years of age and recording carefully each case of mottled enamel, decayed or missing teeth, they postulated that 1 to 1.5 parts of fluorine per million parts of water produced no brown stains of "mottling" and reduced decay by two-thirds.

Although water had been previously fluoridated, it wasn't until 1945 that results of fluoridation of Grand Rapids, Michigan, as a test site with Muskegon, Michigan, as a control, were published. The fluoride concentration of Muskegon which along with Grand Rapids draws its water from Lake Michigan, was to be kept at one-tenth part per million. Aurora, Illinois, whose water contains 1.2 parts of fluorine per million was to be the second control. Again results showed a reduction in tooth decay, particularly in children four to seven years old.

In 1945 a similar test was started in Newburgh and Kingston, New York, both of which get their water from the same source. Newburgh fluoridated and after eight years reports a very significant decrease in dental caries when compared with its control, Kingston. As a result, on February 1, 1953, more than ten million persons in six hundred different cities and towns of the United States were drinking fluoridated water. Since then there has been a reappraisal. Chicago, Milwaukee, and Cleveland have all considered and rejected fluoridation. St. Louis presented fluoridation to its board of aldermen at the beginning of 1953 but the ordinance is gathering dust in its pigeon-hole. A November 6th, 1954 issue of the *Newburgh News* of Newburgh, New York, states that Peekskill, New York, Greenwich, Connecticut, and seven other small communities have followed the lead of the bigger cities in rejecting fluoridation.

The majority of the reports in the literature state that the addition of 1 to 1.2 parts per million of fluorine to drinking water, as advocated by the United States Public Health Service, aids in the delay of dental caries. However, there is some disagreement about just how this is accomplished. For a time it was felt that fluorine prevented decay by lowering the count of *Lactobacillus acidophilus,* the organism in the saliva thought to be responsible for decay. Counts of zero to less than one hundred are found in 38% of the children as compared with 18% in the fluoride areas (5). Consequently, there seems to be no relationship between fluoride content in saliva and incidence in caries. Later, electron and X-ray diffraction experiments showed that the treatment of powdered dental enamel surfaces results in a direct transformation from an apatite to a calcium fluoride crystalline structure; a more resistant form. The rate of the transformation was influenced by the acidity and concentration of fluorine in the solution (6)—for human beings this would be the saliva. At present the mode of action is taken as a combination of both of the preceding theories.

During this time chemists, dentists, and physicians were asking themselves what were the physiological effects of fluoridation. How does this chemical, fluorine, affect the sick and healthy, alike? Was there no effect, was there a beneficial or was there a detrimental effect on the body functions—especially, on the organs such as the liver, heart, kidneys, thyroid, etc., which were already weakened by disease? How would the people fare in a community which was abruptly and completely subjected to fluoridated water? Investigations are slow and costly. Results were and still are dribbling in because the animal organism known as man has a relatively long life span and the abnormalities which are brought about by factors in the environment are very slow but certain in development.

An article written on March 21, 1953 in *Business Week* has this to say (7):

> "Quite a few doctors and scientists want to know just what fluorine does to the bones, to elderly people with chronic diseases, and—on a long-range basis—to teeth. Of a given amount of fluorine absorbed by the body, a much larger percentage goes into the bones than into the teeth. Doctors are wondering whether the larger amounts will not damage bone marrow.

> It has been found in statistics that deaths from certain causes, notably heart attacks, have increased sharply in cities where the water is fluoridated. Scientists think that these figures indicate a danger area that should be explored.
>
> The early research on fluorine showed that it was one of the causes of mottled, or darkened, teeth. This was caused by too high a concentration of the chemical. It is thought that no matter how weak the concentration, continued use of the treated water would permit the body to store up dangerous quantities. . . . The anti-fluoridators claim that however fine the effects may be on the teeth of children, they may be over balanced by troubles when childhood is passed."

Since then the United States Public Health Service has issued a publication with some statistical evidence showing fluoridation does not affect the heart. Close analytical evaluation of this evidence shows it not to be conclusive.

J. Rorty in a 1953 issue of Harper's describes the work and findings of a research dentist (8):

> "Dr. Reuben Feltman, research dentist, conducted a study of children and pregnant women to whom fluoride tablets had been administered (equivalent of one part per million water fluoridation). Many of his subjects had such bad reactions in the form of urticaria, vomiting, etc., that this dosage had to be discontinued. His question is, 'What will happen to such individuals when water is fluoridated if it may cause unusual reactions to a few?'
>
> Dr. Feltman again asks: 'Where are we going? Are we going hastily to fluoridate all water supplies, reduce the incidence of dental caries, and then be stigmatized as a profession because of dental fluorosia which appears after twelve to fourteen years of use and possible other effects which may prove to be serious medical problems after twenty to thirty years of ingestion?' "

Dr. V. O. Hurme (9), Director of Clinical Research, Dr. A. Taylor (10), Research Scientist, Dr. R. S. Harris (11), Director of the Nutritional Biochemistry Laboratories and Dr. G. W. Rapp (12) of the School of Dentistry, Loyola University, are some of the scien-

tists, among others, who believe fluoridation harmful. As recently as June, 1954, V. A. Kleinfeld, Washington lawyer representing the Citizens Committee on Fluoridation at hearings on the Weir Bill in Washington, D. C., charged that not enough is yet known about possible physiological effects of fluoridated water to justify its use by any federal, state, or municipal agency (13).

Fluorine and its compounds have long been known to be poisons. Fluorine as an element is the most active of the halogen family, whose stable other members are chlorine, bromine, and iodine. Sodium fluoride is used as a rat poison and a poisoning agent in many of the preparations on the market today. Calcium fluoride has been used as a roach poison and, hydrogen fluoride, a highly corrosive acid, may be compared with hydrogen cyanide as a lethal agent, especially in the gaseous state. All three of these compounds together with sodium fluorosilicate have been or are being used as an artificial source of fluoride ion in drinking water; sodium fluoride being the principal compound used. The range of acute toxicity of sodium fluoride is from 0.046 to 0.50 milligrams per kilogram of body weight when injected subcutaneously in dogs, rabbits, guinea pigs or rats (14). The acute toxicity range in man is not definite and has yet to be accurately determined although it is suspected that these concentrations are harmful if not toxic.

Analysis has shown fluorine to be present in the body in small amounts and there is some speculation among scientists whether it is a necessary element or is present because it is in our daily food and is deposited along with the calcium and phosphorus of the body. The normal bone contains from 0.01 to 0.03% of fluorine and the dental enamel contains from 0.01 to 0.02%. As has been stated, since no diet has so far been devised which is free of fluorine, it is difficult to determine whether the element has a functional importance, and, if so, what the function is.

An article which dramatically points out the lethal possibilities of fluorides, is entitled "Pass the Arsenic but be Sure to Try the Fluorine as Well" (15). In one of its statements the article points out the fact that an overdose of fluoride, familiar as an ant poisoner, kills one quite as dead as arsenic.

Many communities have drinking water whose fluoride content is greater than the artificially introduced 1.2 parts per million; especially those states in the south and southwestern part of the United

States. In these localities the problem is one of defluorination using activated superphosphate, slaked lime, etc. There is an acknowledged problem in "mottling" of teeth and in preparation of water for industrial use. The breweries are greatly concerned, as are the bakeries, because it has been demonstrated rather thoroughly that the yeast organism is very susceptible to fluorine. Not much has been published correlating the vital statistics with that of other areas having little or no fluorine in their drinking water but one fact has been presented. The ratio of premature births in Texas and New Mexico is 35.1% and 55.9% respectively, as compared with the ratio of 26.7% throughout other sections of the country (16, 17).

In the naturally fluoridated waters calcium fluoride (solubility is 0.17% at 26° C.) and sodium silicofluoride (solubility very low) are the principal fluorine compounds. The chief artificially introduced fluoride, sodium fluoride, has a solubility of 4.0% at 25° C.; although recent experiments have proven stannous fluoride a better fluoridating agent for the delay of dental caries (18). Thus the fluorine available as hydrogen fluoride from calcium fluoride at a concentration of one part per million is 0.00425 milligrams and from sodium fluoride at the same concentration, 0.25 milligrams to a glass of water (19). It can be clearly seen that it is possible for a naturally fluoridated water with a higher per cent of fluorine to give less *available* or *useful* fluorine ion than an artificially fluoridated water.

In addition to the water supply as a source, we get fluorine from many of the common foods in the American diet. From butter, cheese, liver, chicken, oysters, bread and honey we get 1.5, 1.6, 1.5, 1.4, 1.5, 1 and 1 parts per million of fluoride, respectively (20). Dry tea is especially rich in fluoride with a content of thirty to sixty parts per million of fluoride (21). Thus it is easily seen that the amount of fluorine necessary for delay of dental caries and the amount necessary for body function, if necessary at all, is amply supplied in the daily diet.

In highly fluoridated areas, such as Texas and New Mexico, crops that are grown there and shipped to other areas, are found to contain large quantities of fluorine. When boiled and cooked in water which has fluorine present, the fluorine content of the vegetables or cereals increases due to some adsorptive or absorptive mechanism—as well as to evaporation of the water. For example, it has been determined that food cooked in water containing one part of fluorine

per million becomes in twenty minutes of boiling, two parts per million. Such food as oatmeal, cereals, and so on will absorb that additional concentration of artificial fluorides in addition to their own original high content of fluorine.

The concentration is of importance because the greater the amount taken in, the greater the amount absorbed, to a certain level. The duration of time fluorides stay in the system is also a factor in the amount that is absorbed by the system. The hydrogen ion concentration, or pH, of the media is very important; the more acid in the blood or the gastrointestinal system, the more fluoride absorbed. If the fluoride is taken in with slow-absorbing food or with calcium, minerals and vitamins, such as B_1, B_2 or B_6, less of the fluoride is absorbed. If the system, at the time the fluoride is ingested, has a low calcium or mineral content, more of it is absorbed (22).

It has been determined, also, that the age of the individual is important because an infant or child with growing connective tissue absorbs more than an adult or senile person. Secondly, the sex of the individual is a factor. Experiments have proven that females or people with a high metabolic rate absorb more than males or those with a normal metabolic rate. People with a high temperature, such as those with a fever, absorb more fluorine than those with a normal temperature.

People with fevers and healthy people have different reactions. Sufferers from chronic diseases, such as rheumatic fever, diabetes, heart conditions, kidney trouble and blood conditions are known to absorb more fluorine. Again, the weather, humidity, heat or cold have to be considered. The warmer the day, the greater the amount of fluorine ingested. Changes in weather conditions bring about a like change in reservoirs in which artificially fluoridated water is stored; that is, more fluoride ion is available because solubility increases with temperature. Other obscure factors such as the action of radioactive substances and cosmic rays, through radiation, supply energy for a more abundant absorption of fluorine by the human system.

Perhaps the most important factors found in fluorine absorption are the diet and nutritional make-up of an individual. Sodium fluoride is known to have a greater effect on the poorly nourished person who lacks calcium, other minerals, and vitamins because of the greater absorption ratio of sodium fluoride.

Autopsies performed on normal and abnormal individuals show that there is a very minute difference between normal and abnormal concentrations of fluorine in the different parts of the body (23).

	Normal (p.p.m.)	Abnormal (p.p.m.)
Brain	0.6	1.6
Heart	1.6	2.6
Blood	3.5	3.6
Kidneys	4.5	4.6

These results have also strengthened the belief that it is a problem of fluorine activity rather than one of concentration.

Some proof has been found that the calcium, minerals, bones, enzymes, vitamins, cells, endocrine glands, and metabolism of the carbohydrates, the proteins and the fats of the body have been affected. When sodium fluoride is taken into the system, it is absorbed, presumably as fluoride ion, in the upper part of the small intestine. It is then carried by the blood stream to the different cells, organs and tissues in the form of calcium fluoride, robbing the system of calcium.

At the cell some of the fluorine may enter or remain on the outside as an insoluble precipitate affecting the feeding and the breathing. As a result, the cell may lose some of its functions or it may die. Some of the calcium fluoride is carried to the connective tissues and the bones where it is stored. For example, it has been determined that the femur bone may contain fifteen times more calcium fluoride than any other part of the body. Some of the fluoride is excreted through the gastrointestinal tract, some through the urinary tract, some through perspiration and one-tenth part is excreted through the salivary glands. In addition, it has been found that if there is a deficiency of calcium in the system, fluorine will react with other minerals, displacing them from their essential use and neutralize their function to a great extent (24).

Fluorine combines with the metallic portion of the enzyme which is made up of vitamins and proteins. By so doing, it nullifies the enzyme action. Some of the enzymes affected are phosphatase, lipase, transaminase (25), and succincic dehydrogenase (26). One part of fluorine per fifteen million will reduce lipase activity fifty per cent; and there are now indications that it affects adenosine triphosphate—the high energy intermediary compound in carbohydrate metabolism.

Gortner and Gortner say (27):

> "Fluoride ions are known to inhibit enolase, which catalyzes the conversion of 2-phosphoglycerate to enol-2-phosphopyruvate. The fluoride ion in the presence of phosphate forms a magnesium fluorophosphate complex which, by removal of magnesium from combination with the enzyme, results in the inhibition of the reaction. The use of fluoride as an inhibitor of glycolysis allows isolation and identification of the precursors of phosphopyruvate that accumulate, in particular 3-phosphoglycerate and hexose phosphates. Fluoride will inhibit many enzymes, particularly those requiring magnesium ions."

Fluorine prevents the absorption or assimilation of vitamins B_1 B_2 and B_6, and prevents the storage of Vitamin C. It affects the cytochrome-oxidative system of the cells and interferes with the action of the thyroid. (28).

There are experiments showing that fluorine interferes with nitrogen, phosphorous and calcium metabolism. Studies of rats on a normal diet and on a 5% protein diet with the ingestion of at least two milligrams of sodium fluoride per day showed a decrease in the retention of nitrogen, phosphorus and calcium. The rate of absorption of these elements was decreased and their rate of excretion increased (29). Oxidative metabolic studies using mouse stomach and mucosa showed that the oxygen uptake was inhibited by fluorides as well as other compounds (30).

There are strong indications that fluorine interferes with purine metabolism so that an accumulation of uric acid is formed with the possible formation of kidney stones and possible causation of gout. There is an increase of cholesterol in the blood and, if the fluoride reacts with acetic acid, forming fluoroacetic acid (31), it will prevent the breakdown of citric acid into other compounds. Citric acid is a poison which is injurious to heart muscle.

Studies of approximately five hundred cases at the Brusch Medical Center showed everyone to be allergic to sodium fluoride—from a mild to severe reaction, depending on their inherent rate of sensitivity. The Healy Blood Allergic Diagnostic Test Method was used. This work is done directly on samples of venous blood with equal parts of tap water and depends upon fractional precipitation of phosphates. This same salting-out process occurs in the body and inhala-

tion, contact with, or ingestion of fluorides may be readily verified rather dramatically by the Healy Method.

The blood of people living in naturally fluoridated areas takes six to twenty times longer to coagulate. Calcium ions are known to play an important role in blood clotting. Therefore, many have assumed that continual ingestion of fluorides has resulted in a depletion of the calcium supply; causing a longer clotting time. This fact has been proven in the test tube but has yet to be proven for human beings, probably because of the low concentration of fluorine used in fluoridation (32). One series of experiments has given positive results, showing that ingestion of three milligrams of fluorine per kilogram of body weight produces a severe anemia and a decrease in the serum phosphatase content (33).

Continual subjection to fluorides, uric acid, or stone formation impairs or damages the kidneys so that they cannot excrete either fluorides or other wastes. It has been experimentally determined that fluorides stimulate low concentrations of urea in the Krebs-Henseleit cycle. Complete inhibition occurs at five hundredths molarity (34).

It is known that chronic fluorine poisoning affects the section of the brain concerned with volition and the will to resist. The same area is affected by hypnotism. Inhibition of phosphatase exerts progressive degenerative changes on the nerv tissue throughout the body by altering the phosphorous-calcium ratio and inhibiting the utilization of vitamin B_1. It affects, also, the cerebral area to a large extent. Experiments with rats showed a marked deterioration in mental alertness, accompanied by a state of passiveness and bewilderment. In addition, there is a question of increase in eye diseases due to artificial fluoridation. In Washington, D. C., fluoridated without legislation or permission, more cases of glaucoma are being reported. As yet there are no definite statistics proving the relationship between the two.

In some cases various writers have compared fluoridation to our present process of chlorination to kill bacteria in water. No comparison could be more erroneous. First of all, the avowed purpose of fluoridation is to prevent, as much as possible, decay in the teeth of children, and not to make water safe for drinking. Secondly, although both as elemental gases are poisonous, there is a great difference in the toxicity of their compounds. Sodium chloride and calcium chloride, for example, are not as toxic as sodium fluoride or calcium fluoride. We use sodium chloride, table salt, daily as an essential

constituent of the diet whereas sodium fluoride taken in the same amounts daily would be extremely poisonous. The comparison may be carried further with but the same exhibition of fluoride toxicity.

The United States Public Health Service is one of the chief proponents of fluoridation. They admit that there are a number of arguments with which they are powerless to cope. For example, Dr. Bull of the P. H. S. says (35): (in response to Dr. Glover Jones of Texas, on the question of fluorine in water supplies causing cancer in mice)

> "I wish I knew the answers. . . . I do not know why they didn't include a letter from two-thirds of the deans of the dental schools of the Universities saying that fluoridation is rat poison, and should not be used. I think you are fortunate you have only that one thing, because we have had many more. . . . You know these research people—they cannot get over the feeling that you have to have test tubes before you start applying it to human beings."

In response to Dr. David Ast of New York wondering if the University of Texas might refute their statement on fluorine causing cancer in mice, this was the response:

> "There is this doctor, when I was talking about refuting this thing I did not mean bringing it up and knocking it down. When this thing came out we never mentioned it in Wisconsin. All we did was to get some publicity on the fact that there is less cancer and less polio in high fluoride areas. We got that kind of information out to the public, so that if the opposition did bring up the subject they would be on the defensive, rather than having us on the defensive."

After the significant statement about polio had been made, in 1952, Texas, a high fluorine area, had one of the worst outbreaks of polio in its history.

Particularly enlightening is an example of the manner in which the P. H. S. "sells" its program of fluoridation to the public

> "Well, from your state level you can have a man come in who knows how to present fluoridation, and let me tell you this, the medical audience is the easiest audience in the world to present this to. . . . So you come out with a resolution from your county or local board of health. Next go before lay groups,

service clubs, P. T. A.s and always invite the public officials, water men, aldermen, mayors anybody you can get . . . sort of a lobbying procedure you are carrying on.

Have the press at every one of those meetings . . . now where dentists do not seem interested, do not let that stymie you . . . what we do in a case like this is to arrange for the P. T. A. or some group to ask for some of us to come in and talk about fluoridation. In this way you get in without forcing yourself . . . and you can build a fire under the dentists. That is promotional work . . . you have to knock their objections down. The question of toxicity is on the same order. Lay off it altogether. Just pass it over.

Let me tell you the P. T. A. is a honey when it comes to fluoridation. Give them all you have got."

Therefore, in conclusion, we have evidence that in the delay of dental caries in children, fluoride treatment is helpful, but even here there is contradictory evidence from dental researchers and, there is the defect that when the critical level of fluoride is overstepped, unsightly mottling results. However, since no contagious disease is involved this is not a public health problem but a personal matter. Such fluoridation would impose upon the entire population the consumption of highly toxic protoplasmic poison in small doses from the time before we are born until the time we die. This drug, against which there is no antidote, would be forced on everyone, regardless of his environment, his physical condition and his moral attitude—whether or not he wishes to take this drug. At the same time, there might be created a false sense of security, a false impression that we do not need to consider the predisposing causes, the bacterial, nutritional or the hygienic procedures under medical and dental care which are essential for good teeth.

However, what is to be greatly feared is the long-term results of fluoridation on the physiological system. We know that fluoride effect is a matter of activity, that is, how much is available as fluoride ion and not as some insoluble complex as calcium fluoride, which is the main constituent of "natural" fluoridated waters. We know that the oft repeated statement, "other people live in areas in which the natural fluorine content of the water is much higher than one part per million and they suffer no ill effects", is not true. Investigations

of the vital statistics of those areas have been in progress and some of the reports trickling in, show some startling correlations with harmful physical dysfunction and abnormalities. This is particularly true for heart disease, premature births, osseous growth and cancer (36, 37). Scientific proof or disproof of these facts will take time and cannot be dismissed with a refutation like that published recently by the United States Public Health Service regarding heart disease.

Experiments performed and studies already made on animals, and, in some cases man, definitely indicate that fluoridation is harmful. We do not have enough data to date to know exactly what does happen. Enough has been done, however, to strongly indicate that even at a concentration of one part per million fluorine has a cumulative toxicity, much in the same manner as arsenic, on people with defective excretory organs.

Principally, for these reasons there are now militant organizations of citizens in almost every community who oppose fluoridation as was most recently shown in St. Louis. One such committee which represents Florida has petitioned congress to pass the anti-fluoridation Weir Bill because (38):

> "It is unethical and illegal for city councils and water works departments, who are unlicensed, to prescribe medical treatment or to dispense treatment to anyone individually or *en masse*.
>
> We insist upon exercise of our right to be secure in our own homes and persons, to choose our own physicians, our own medicine and manner of taking it."

For those who wish to provide enough fluorine to insure getting the amount prescribed by the Public Health Service they have the choice of selecting certain foods for the diet or they may apply any of the several brands of tooth paste or dental powder containing fluoride which is on the market. Let them not gamble with the lives of their children and loved ones by allowing the ingestion of fluoride to become mandatory. It would be wise to heed the words of the Right Reverend Monsignor Thomas J. Riley who said in his newspaper column (39):

> "As long as, in the judgment of competent authorities, there is solid reason for fearing that fluoridation may have serious, harmful and widely prevalent long-term effects, it would be wrong to impose it on the general population."

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SELECTED ABSTRACTS

Ointment and Cream Formulations With Silicones. Malloch, M. M. *Pharm. J. 173:*140 (1954). Several silicone formulations were suggested by the author. The compounding of silicones in ointments and creams was not found to be difficult. In general, the oil phase was fused wtih the silicone fluid on a water-bath, the aqueous phase was heated to approximately the same temperature, the two phases were mixed, and then stirred until cool.

The silicone employed in these formulations was a methyl silicone having a viscosity of 350 centistokes and designated as MS 200. The following formula was found to be greasy but to have very good water-repellent properties:

MS 200	30 per cent
Cetyl alcohol	10 per cent
Yellow petrolatum	60 per cent

The silicone was found to separate if incorporated with only the petrolatum. A vanishing cream type of preparation having good water repellency has the following formula:

MS 200	70 per cent
Magnesium stearate	30 per cent

A vanishing cream type of preparation having pleasing cosmetic properties and which can be diluted with water, has the following formula:

MS 200	30 per cent
Stearic acid	5 per cent
Cetyl alcohol	2 per cent
Diethylene glycol monoethyl ether	10 per cent
Water q.s. to make	100 per cent

The proportion of silicone in the formula can also be varied, particularly upward, without markedly affecting the stability or cosmetic acceptability of the preparation.

An Evaluation of Polyvinylpyrrolidone as a Retardant Agent for Penicillin. Milberg, M. B., Colsky, J. and Lerner, S. *Antibiot. and Chemother. 4*:871 (1954). The authors sought to evaluate the retardant action of polyvinylpyrrolidone (PVP) on the absorption of penicillin. Such effect had been reported for PVP by other authors.

The plan followed in this study was to administer a prescribed dose of penicillin in physiological saline and then determine the penicillin blood levels over specified intervals. The next day the same plan was followed except that the penicillin was dissolved in an equal volume of 10 per cent PVP solution. Four patients were given crystalline potassium pencillin G intramuscularly in a dose of 500,000 units. The serum levels were generally higher during the first 4 hours when the vehicle was PVP solution and were detectable for 8 hours as compared with 4 hours when the vehicle was saline.

Three patients were given 500,000 units of crystalline potassium penicillin G in 10 cc. and 9 patients in 250 cc. of physiological saline by the intravenous route. When the same procedure was followed using 10 per cent PVP solution as the vehicle there was no significant difference in the blood levels obtained. Nine patients were given 300,000 units of procaine penicillin G intramuscularly, using first physiological saline and then 20 per cent PVP solution. While the blood levels were higher in some cases where the PVP solution was used there was no consistency in the elevation or prolongation of the blood levels. In no case was there any indication of untoward reactions attributable to PVP.

The authors suggested that further studies should be conducted in regard to this matter. They felt that intramuscular injections of crystalline penicillin G in PVP solution might prove to be a means of raising and prolonging the blood levels of penicillin obtained.

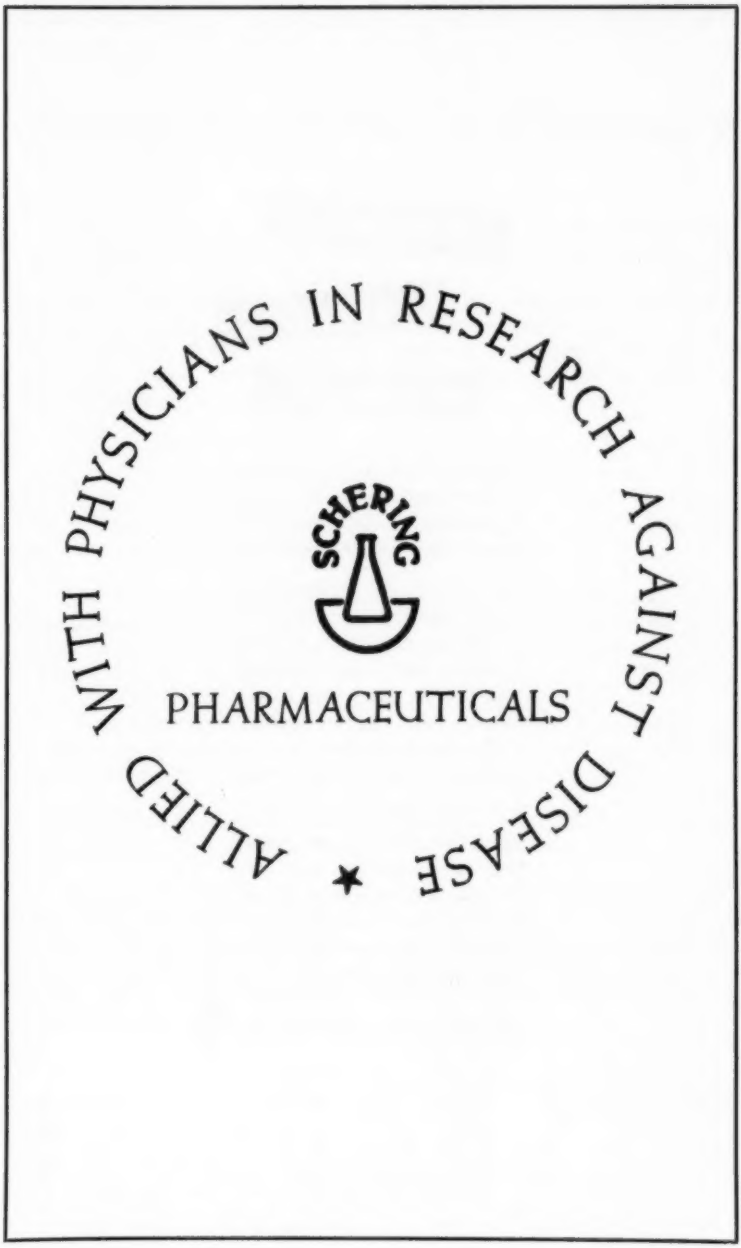
BOOK REVIEW

Organic Chemistry, Second Edition. By Reynold C. Fuson and H. R. Snyder. John Wiley and Sons, Inc., New York, 1954. vii + 544 pp. Price $6.50.

The second edition, of the now well known book, is patterned after the first edition. Aliphatic, alicyclic and aromatic compounds are treated together and the text is sectioned according to functional group rather than structure. The material has been brought up to date, especially the chapter on polymerization and polymers. Not too much information is included on reaction mechanisms and therefore only a feeble attempt is made to convince the student that quite a few reactions can be predicted without resorting to brute memory.

The wealth of information contained in the text would make the book appear much too comprehensive for the beginning student, but certainly is advantageous for anyone expecting to go further than a short undergraduate course in organic chemistry.

A. R. GENNARO.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persistent

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The other six danger signals are —Any sore that does not heal ...A lump or thickening in the breast or elsewhere...Unusual bleeding or discharge...Any change in a wart or mole... Persistent indigestion or difficulty in swallowing...Any change in normal bowel habits.

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